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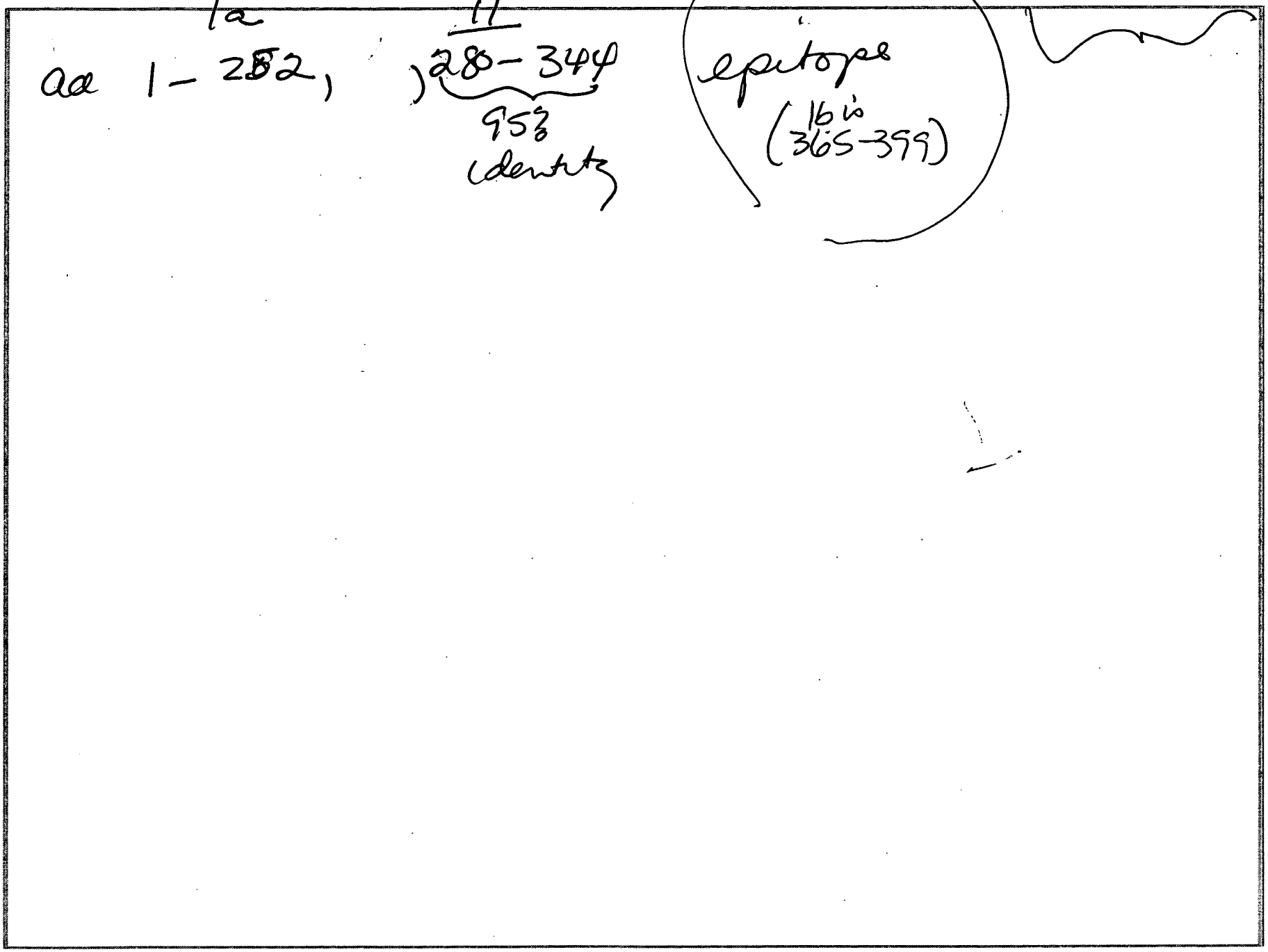
☐	L3	L2 and ($toxin or toxi$).clm.	25
☐	L2	L1 and (pseudomonas or pseudo-monas or pe)	196
☐	L1	(fitzgerald$.in. or Fitzgerald$.in.)	4864

END OF SEARCH HISTORY

Brief Summary Text:
[0013] In another aspect, the invention provides a chimeric protein comprising: (a) a non-toxic Pseudomonas exotoxin A sequence comprising domain Ia, domain II, and domain III; and (b) a Type IV pilin loop sequence, wherein the Type IV pilin loop sequence is located between domain II and domain III of the non-toxic Pseudomonas exotoxin A sequence.

Brief Summary Text:

Search notes



Description of Disclosure:

[0029] "Pseudomonas exotoxin A" or "PE" is secreted by P. aeruginosa as a 67 kDa protein composed of three prominent globular domains (Ia, II, and III) and one small subdomain (Ib) connecting domains II and III. (Allured et. al., Proc. Natl. Acad. Sci. 83:1320-1324 (1986).) Domain Ia of PE located at the N-terminus and mediates cell binding. In nature, domain Ia binds to the low density lipoprotein receptor-related protein ("LRP"), also known as the .alpha.2-macroglobulin receptor (".alpha.2-MR"). (Kounnas et al., J. Biol. Chem. 267:12420-23 (1992).) It spans amino acids 1-252. Domain II mediates translocation to the cytosol. It spans amino acids 253-364. Domain lb has no known function. It spans amino acids 365-399. Domain III is responsible for cytotoxicity and includes an endoplasmic reticulum retention sequence. It mediates ADP ribosylation of elongation factor 2 ("EF2"), which inactivates protein synthesis. It spans amino acids 400-613. The native Pseudomonas aeruginosa exotoxin A nucleic acid sequence and the amino acid sequence are shown as SEQ ID NO:1 and SEQ ID NO:2, respectively. SEQ ID NOS: 1 and 2 are the mature form of exotoxin A, wherein the signal sequence has been cleaved off. As a virulence factor, PE can kill PMNs, macrophages and other elements of the immune system (Pollack et al., Infect. Immuno. 19(3):1092-6 (1978)).

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Search Results - Record(s) 1 through 25 of 25 returned.

☐ 1. 20070003578. 15 May 06. 04 Jan 07. Chimeric protein comprising non-toxic pseudomonas exotoxin and type IV pilin sequences. Fitzgerald; David J. . 424/236.1; 424/260.1 A61K39/108 20060101

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TOXIN	42458
ATOXIN	2
COBATOXIN	2
TUBATOXIN	1
PHYTOLACCATOXIN	10
SECATOXIN	1
TAICATOXIN	18
KDATOXIN	1
HETEROPODATOXIN	1
THYMELEATOXIN	20
(L2 AND ($TOXIN OR TOXI$).CLM.).PGPB,USPT,USOC,EPAB,JPAB,DWPI,TDBD.	25

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-continued

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35:

Lys Asp Glu Leu
1

(2) INFORMATION FOR SEQ ID NO:36:

(i) SEQUENCE CHARACTERISTICS:
(A) LENGTH: 6 amino acids
(B) TYPE: amino acid
(C) STRANDEDNESS:
(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: peptide

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:

Gly Trp Glu Gln Leu Glu
1 5

What is claimed is:

1. A protease-activatable Pseudomonas exotoxin A-like ("PE-like") proprotein comprising:

(a) a cell recognition domain that binds to an exterior surface of a targeted cell;

(b) a modified PE translocation domain comprising an amino acid sequence with 80% or greater sequence identity to amino acids 280 to 344 of SEQ ID NO:2 and which effects translocation to a cell cytosol upon proteolytic cleavage, wherein the translocation domain comprises a cysteine-cysteine loop that comprises a protease activatable sequence cleavable by a protease and wherein the protease activatable sequence is refractory to cleavage by furin when incubated with furin at a 1:10 enzyme:substrate molar ratio at 25° C. for 16 hour;

(c) a cytotoxicity domain comprising an amino acid sequence with 80% or greater sequence identity to amino acids 400 to 613 of SEQ ID NO:2, the cytotoxicity domain having ADP-ribosylating activity; and

(d) an endoplasmic reticulum ("ER") retention sequence.

2. The PE-like proprotein of claim 1 wherein the modified PE translocation domain has a PE domain II sequence (amino acids 253–364 of SEQ ID NO:1) modified with amino acids substitutions introducing the protease activatable sequence so as to cause cleavage by the protease between amino acids 279 and 280.

3. The PE-like proprotein of claim 1 wherein the protease activatable sequence is cleavable by a protease secreted by a cancer cell.

4. The PE-like proprotein of claim 1 wherein the cell recognition domain comprises an antibody that specifically binds to a cancer cell surface marker.

5. The PE-like proprotein of claim 2 wherein the protease activatable sequence is cleavable by prostate specific antigen ("PSA").

6. The PE-like proprotein of claim 2 wherein the protease activatable sequence is cleavable by urokinase.

7. The PE-like proprotein of claim 2 wherein the protease activatable sequence is cleavable by neutral endoprotease, stromelysin, collagenase, cathepsin B, or cathepsin D.

8. The PE-like proprotein of claim 2 further comprising a PE Ib domain, and wherein said PE Ib domain, the cytotoxicity domain, and the ER retention sequence together have the sequence of domains Ib and III of native PE.

9. The PE-like proprotein of claim 3 wherein the cell recognition domain is coupled to the modified translocation domain through a peptide bond.

10. The PE-like proprotein of claim 5 wherein the protease activatable sequence is SKGSFSIQYTYHV (SEQ ID NO:11), HLGGSQQLLHNKQ (SEQ ID NO:12), or SKGKGTSSQYSNTE (SEQ ID NO:13).

11. The PE-like proprotein of claim 6 wherein the protease activatable sequence is DRVYIHPF (SEQ ID NO:3), VVCGERGFFYTP (SEQ ID NO:4), FFYTPKA (SEQ ID NO:5), KRRPVKVYP (SEQ ID NO:6), PVGKKRRPVKVY (SEQ ID NO:7), KPVGKKRRPVKV (SEQ ID NO:8), GKPVGKKRRPVK (SEQ ID NO:9), or TFAGNAVRRSVGQ (SEQ ID NO:10).

12. The PE-like proprotein of claim 8 wherein the cell recognition domain is an antibody coupled to the modified translocation domain through a peptide bond and wherein the antibody specifically binds a cancer cell surface marker.

13. A composition comprising a pharmaceutically acceptable carrier and a therapeutically effective amount of a protease-specific Pseudomonas exotoxin A-like ("PE-like") proprotein comprising:

(a) a cell recognition domain that binds to an exterior surface of a targeted cell;

(b) a modified PE translocation domain comprising an amino acid sequence with 80% or greater sequence identity to amino acids 280 to 344 of SEQ ID NO:2 and which effects translocation to a cell cytosol upon proteolytic cleavage, wherein the translocation domain comprises a cysteine-cysteine loop that comprises a protease activatable sequence cleavable by a protease and wherein the protease activatable sequence is substantially un-activatable by fibrin when incubated with furin at a 1:10 enzyme:substrate molar ratio at 25° C. for 16 hours;

(c) a cytotoxicity domain comprising an amino acid sequence with 80% or greater sequence identity to amino acids 400 to 613 of SEQ WD NO:2, the cytotoxicity domain having ADP-ribosylating activity; and

(d) an endoplasmic reticulum ("ER") retention sequence.

14. The composition of claim 13, further comprising a PE Ib-like domain, wherein:

(a) the cell recognition domain is an antibody coupled to the modified PE translocation domain through a peptide bond and wherein the antibody specifically binds a cancer cell surface marker;

(b) the modified PE translocation domain has a PE domain II sequence (amino acids 253–364 of SEQ ID

NO:1) modified with amino acids substitutions introducing the protease activatable sequence so as to cause cleavage by the protease between amino acids 279 and 280; and

(c) the PE Ib-like domain, the cytotoxicity domain and the ER retention sequence together have the sequence of domains Ib and III of native PE.

15. The composition of claim **14** wherein the protease activatable sequence is cleavable by prostate specific antigen or urokinase.

16. A method for killing a cancer cell comprising contacting the cell with a protease-specific Pseudomonas exotoxin A-like ("PE-like") proprotein comprising:

(a) a cell recognition domain that binds to an exterior surface of a targeted cell;

(b) a modified PE translocation domain comprising an amino acid sequence with 80% or greater sequence identity to amino acids 280 to 344 of SEQ ID NO:2 and which effects translocation to a cell cytosol upon proteolytic cleavage, wherein the translocation domain comprises a cysteine-cysteine loop that comprises a protease activatable sequence cleavable by a protease and wherein the protease activatable sequence cysteine-cysteine loop is substantially un-activatable by furin when incubated with furin at a 1:10 enzyme-:substrate molar ratio at 25° C. for 16 hours;

(c) a cytotoxicity domain comprising an amino acid sequence with 80% or greater sequence identity to amino acids 400 to 613 of SEQ ID NO:2, the cytotoxicity domain having ADP-ribosylating activity; and

(d) an endoplasmic reticulum ("ER") retention sequence.

17. The method of claim **16** wherein the cancer cell is a prostate cancer cell.

18. The method of claim **16** wherein the cancer cell is a colon cancer cell.

19. The method of claim **16** used in the treatment of a subject suffering from cancer.

* * * * *

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Ala Leu Leu Arg Val Tyr Val Pro Arg Ser Ser Leu Pro Gly Phe Tyr
            500                 505                 510

Arg Thr Ser Leu Thr Leu Ala Ala Pro Glu Ala Ala Gly Glu Val Glu
        515                 520                 525

Arg Leu Ile Gly His Pro Leu Pro Leu Arg Leu Asp Ala Ile Thr Gly
    530                 535                 540

Pro Glu Glu Glu Gly Gly Arg Leu Glu Thr Ile Leu Gly Trp Pro Leu
545                 550                 555                 560

Ala Glu Arg Thr Val Val Ile Pro Ser Ala Ile Pro Thr Asp Pro Arg
                565                 570                 575

Asn Val Gly Gly Asp Leu Asp Pro Ser Ser Ile Pro Asp Lys Glu Gln
            580                 585                 590

Ala Ile Ser Ala Leu Pro Asp Tyr Ala Ser Gln Pro Gly Lys Pro Pro
        595                 600                 605

Arg Glu Asp Leu Lys
    610
```

What is claimed is:

1. A method of making a cell toxin comprisng

reacting a polypeptide comprising a *Pseudomonas* exotoxin translocation domain linked to a *Pseudomonas* exotoxin ADP-ribosylatin domain, wherein the *Pseudomonas* exotoxin translocation domain comprises at least one reactive sulfhydryl group, with a substance P peptide comprising one additional cysteine residue at its amino terminal end, wherein the cysteine sulfhydryl group is disulfide linked to a di-thiobis (2-nitro)-benzoic acid group, such that after the reaction a disulfide bond is formed between the exotoxin polypeptide and the substance P and a thionitrobenzoate group is released, and

purifying the substance P-*Pseudomonas* exotoxin disulfide linked conjugate from the released thionitrobenzoate group such that the purified conjugate is substantially free of thionitrobenzoate groups.

2. The method of claim 1, wherein the *Pseudomonas* exotoxin translocation domain sulfhydryl group located within ten amino acid residues of the translocation domain amino terminus.

3. The method of claim 1, wherein the *Pseudomonas* exotoxin translocation domain sulfhydryl group located at the translocation domain amino terminus.

4. The method of claim 1, wherein the *Pseudomonas* exotoxin translocation domain sulfhydryl group is a cysteine residue.

5. The method of claim 1, wherein the *Pseudomonas* exotoxin translocation domain is covalently linked to the *Pseudomonas* exotoxin ADP-ribosylation domain.

6. The method of claim 5, wherein the covalent linkage between the Pseudomonas exotoxin translocation domain and the *Pseudomonas* exotin ADP-ribosylation domain is a peptide bond.

7. The method of claim 1, wherein the *Pseudomonas* exotoxin translocation domain comprises an amino acid sequence as set forth in SEQ ID NO:1 and the Pseudomonas exotoxin ADP-ribosylation domain comprises an amino acid sequence as set forth in SEQ ID NO:2.

8. A pharmaceutical composition for the ablation of NK1 receptor expressing cells comprising a cell toxin and a pharmaceutically acceptable excipient,

wherein the cell toxin is a substance P-*Pseudomonas* exotoxin disulfide linked conjugate made by a process comprising the following steps:

reacting a polypeptide comprising a *Pseudomonas* exotoxin translocation domain linked to a *Pseudomonas* exotoxin ADP-ribosylation domain, wherein the *Pseudomonas* exotoxin translocation domain comprises at least one reactive sulfhydryl group, with a substance P peptide comprising one additional cysteine residue at its amino terminal end, wherein the cysteine sulfhydryl group is disulfide linked to a di-thiobis (2-nitro)-benzoic acid group, such that after the reaction a disulfide bond is formed between the exotoxin polypeptide and the substance P and a thionitrobenzoate group is released, and

purifying the substance P-*Pseudomonas* exotoxin disulfide linked conjugate from the released thionitrobenzoate group such that the purified conjugate is substantially free of thionitrobenzoate groups.

9. The pharmaceutical composition of claim 8, wherein the *Pseudomonas* exotoxin translocation domain sulfhydryl group located within ten amino acid residues of the translocation domain amino terminus.

10. The pharmaceutical composition of claim 8, wherein the *Pseudomonas* exotoxin translocation domain sulfhydryl group located at the translocation domain amino terminus.

11. The pharmaceutical composition of claim 8, wherein the *Pseudomonas* exotoxin translocation domain sulfhydryl group is a cysteine residue.

12. The pharmaceutical composition of claim 8, wherein the *Pseudomonas* exotoxin translocation domain is covalently linked to the *Pseudomonas* exotoxin ADP-ribosylation domain.

13. The pharamceutical composition of claim 12, wherein the covalent linkage between the *Pseudomonas* exotoxin translocation domain and the *Pseudomonas* exotoxin ADP-ribosylation domain is a peptide bond.

14. The pharmaceutical composition of claim 8, wherein the *Pseudomonas* exotoxin translocation domain comprises an amino acid sequence as set forth in SEQ ID NO:1 and the *Pseudomonas* exotoxin ADP-ribosylation domain comprises an amino acid sequence as set forth in SEQ ID NO:2.

15. The pharmaceutical composition of claim 8, wherein the cell toxin and pharamceutically acceptable excipient are

suitable for administration intrathecally, subdurally or directly into the brain parenchyma.

16. A method for ablating an NK1 receptor expressing cell in a patient comprising administering to said patient a cell toxin in a pharmaceutically acceptable excipient in an amount sufficient to ablate an NK1 receptor expressing cell,

wherein the cell toxin is a substance P-*Pseudomonas* exotoxin disulfide linked conjugate made by a process comprising the following steps:

reacting a polypeptide comprising a *Pseudomonas* exotoxin translocation domain linked to a *Pseudomonas* exotoxin ADP-ribosylation domain, wherein the *Pseudomonas* exotoxin translocation domain comprises at least one reactive sulfhydryl group, with a substance P peptide comprising one additional cysteine residue at its amino terminal end, wherein the cysteine sulfhydryl group is disulfide linked to a di-thiobis (2-nitro)-benzoic acid group, such that after the reaction a disulfide bond is formed between the exotoxin polypeptide and the substance P and a thionitrobenzoate group is released, and

purifying the substance P-*Pseudomonas* exotoxin disulfide linked conjugate from the released thionitrobenzoate group such that the purified conjugate is substantially free of thionitrobenzoate groups.

17. The method of claim 16, wherein the ablated NK1 receptor expressing cell is a dorsal horn cell, a stratum cell or a brain parenchyma cell.

18. A method of treating chronic pain without significantly afflecting basal nociceptive responses comprising administering to a subject in need thereof a cell toxin in a pharmaceutically acceptable excipient in an amount sufficient to treat chronic pain without significantly afflecting basal nociceptive responses,

wherein the cell toxin is a substance P-*Pseudomonas* exotoxin disulfide linked conjugate made by a process comprising the following steps:

reacting a polypeptide comprising a *Pseudomonas* exotoxin translocation domain linked to a *Pseudomonas* exotoxin ADP-ribosylation domain, wherein the *Pseudomonas* exotoxin translocation domain comprises at least one reactive sulfhydryl group, with a substance P peptide comprising one additional cysteine residue at its amino terminal end, wherein the cysteine sulfhydryl group is disulfide linked to a di-thiobis (2-nitro)-benzoic acid group, such that after the reaction a disulfide bond is formed between the exotoxin polypeptide and the substance P and a thionitrobenzoate group is released, and

purifying the substance P-*Pseudomonas* exotoxin disulfide linked conjugate from the released thionitrobenzoate group such that the purified conjugate is substantially free of thionitrobenzoate groups.

19. The method of claim 18, wherein cell toxin is administered to epineurium cells, perineurium cells, nerve ganglia, nerve sheathers, nerve linings, meninges, pia mater cells, arachnoid membrane cells, dura membrane cells, cells lining a joint or brain or spinal cord parenchymal cells.

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